Lawrence Livermore National Laboratory

Biology & Biotechnology Research Program

Introductions

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Livermore Biosciences
Our Vision and Our Mission

Enhancing the nation's health and security through technological innovation in the biosciences.

Livermore conducts multidisciplinary bioscience of high national importance. Our primary roles are to:

- **apply our expertise in support of national security and other laboratory programs;**
- **improve our understanding of the genome and its relationship to disease susceptibility; and**
- **advance healthcare.**

We execute our roles through synergistic, integrated programs that apply our competencies in genomics, structural biology, biomarkers, bioinstrumentation, bioinformatics, and computational biology.

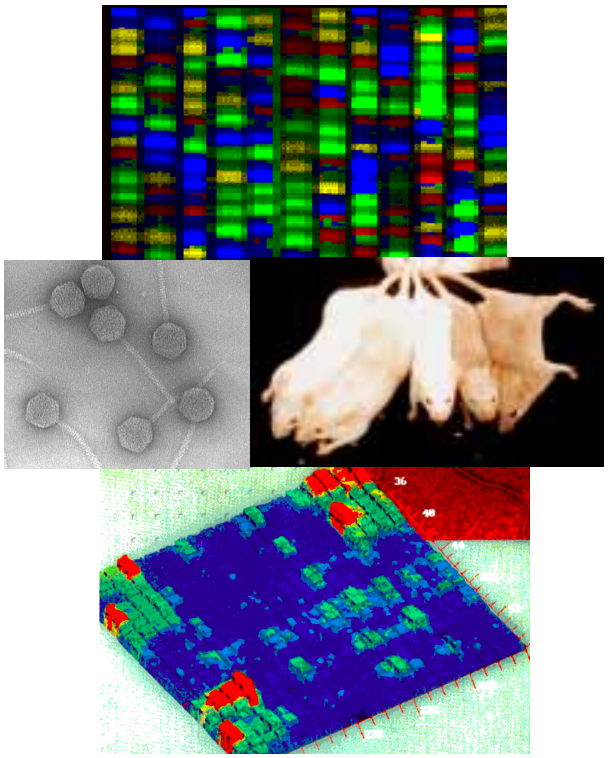
We leverage the laboratory's exceptional capabilities in the physical and engineering sciences.

We partner with universities and industry.

Livermore Biosciences

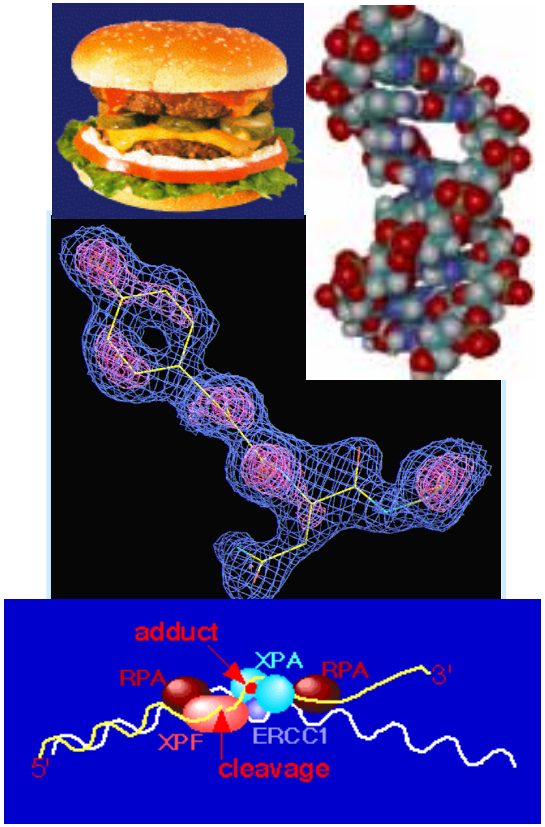
Enhancing the nation's health and security through technological innovation in the biosciences.

Genomics



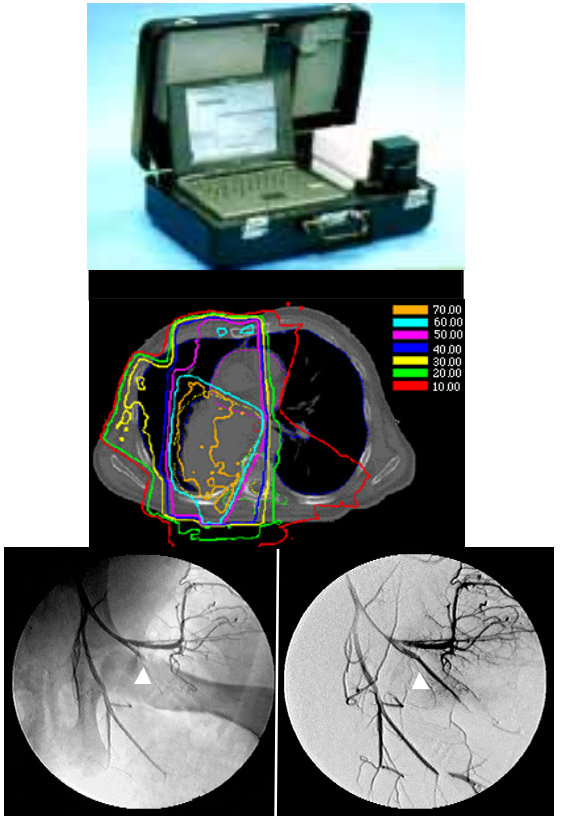
DNA Sequencing
Gene Discovery
Comparative Genomics
Disease Diagnostics

Disease Susceptibility & Prevention



Toxicology & Pharmacology
Structural Biology
Computational Biochemistry
Biochemistry of DNA Repair

Bioengineering & Healthcare Technologies



Microfabrication
Robotics/Lab Automation
Medical Devices

Why is there a Genome Project?

- Estimated to be 100,000 human genes

  Less than 8% of these genes have been identified

- There are about 3 billion bases (information bits) in the sequence of human DNA

  Less than 10% of the sequence has been completed (A G C T)

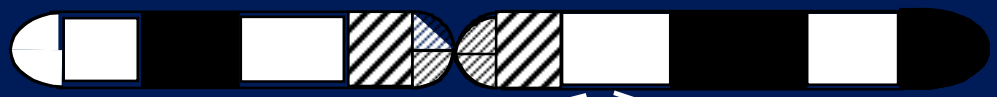
- A focused program to find all the genes and sequence the DNA is more cost effective than a search for one gene at a time
- Even though only 5-10% of our DNA codes for genes, the rest might not be junk!

Deciphering the genomes of humans, plants, animals, and microbes provides the basis for better medical care and an improved quality of life

The Human Genome Initiative: DNA Sequence

DNA Sequence

The order of the four chemical units (nucleotides/bases: A, C, G, T) that comprise the genetic code.



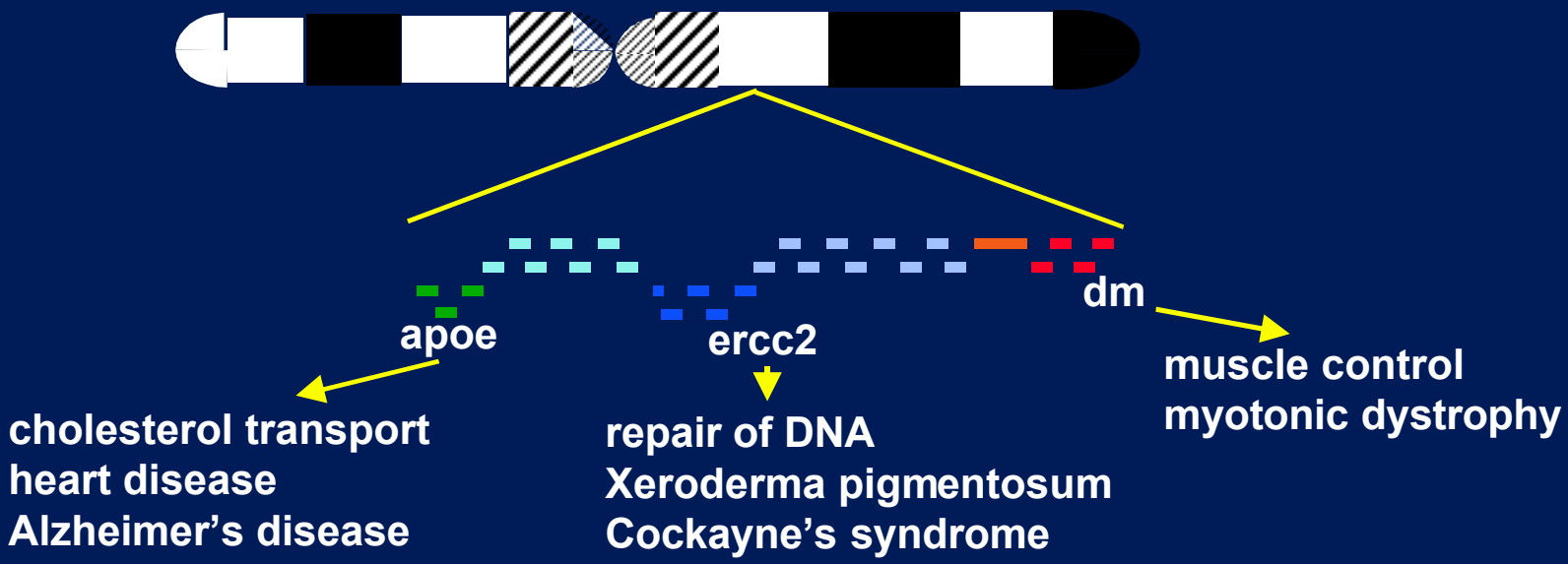
ATGCTTTGGAGAACACAGAGACTTGGGGGATGGGTTGGT
TACGAAACCTCTTGTGTCTCTGAACCCCCTACCCAACCA

Goal: 3.2 billion highly accurate bases (entire genome) by 2003
Attained: approx. 360 million bases in database (11% of the genome)

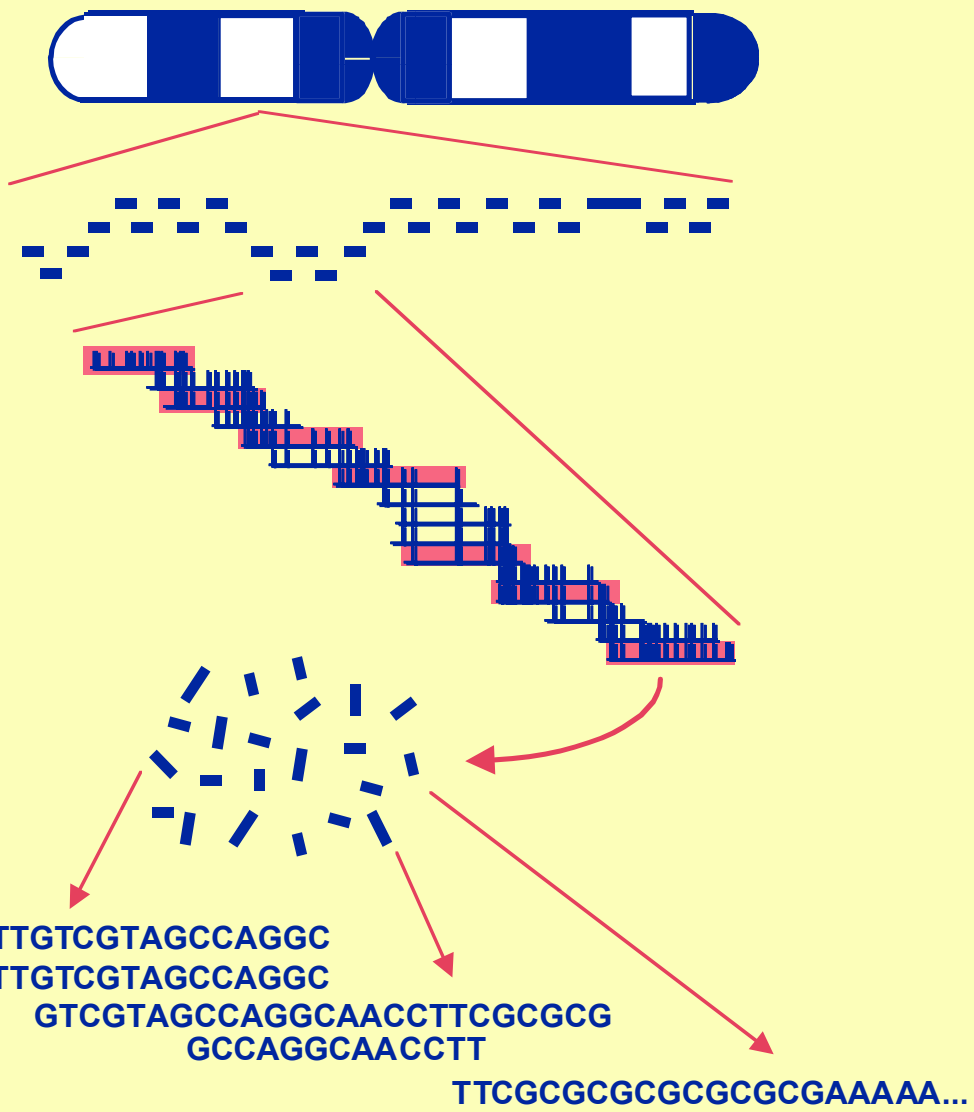
The Human Genome Initiative: Genes & Diseases

Gene Discovery

The location of genes on the chromosome relative to known linkage markers and clones.



Goal: 60,000-100,000 mapped genes by ?
Attained: approx. 5300 mapped genes
(~ 5% of the genome)



Chromosome

Physical Map

Restriction Mapped Contig **- a set of overlapping clones in the physical map**

(map clones selected for sequencing are highlighted)

Sub-clones **for sequencing ("random" pieces of the map clone which are sequenced)**

Assembly **of the sequence from the sub-clones to create *contiguous* sequence of the map clone *(closure)***

Submission of *annotated clone sequence* to the database

THE SUNDAY TIMES

THE VALLEY

SUNDAY, JANUARY 17, 1999 And the Bay Area PAGE A21

Gene project moves to new home

■ Researchers hope the relocation will help them reach a goal of discovering DNA's sequence faster

By Andrea Widener
TIMES STAFF WRITER

WALNUT CREEK — The world's third-largest publicly funded push to uncover the secrets of the human body has almost completed its move into a new production facility.

The move, which began in earnest last month, should help the U.S. Department of Energy reach its lofty goal of revealing 25 times more of the body's instruction book than last year — its contribution to the worldwide Human Genome Project.

In the Shadelands Business Park facility, about 150 researchers from Lawrence Livermore and Lawrence Berkeley laboratories will further expose the pattern of genes that determine everything from our hair color to our tendency toward certain diseases, such as diabetes, asthma and schizophrenia.

The researchers, who are quickly getting back up to speed after their move, are sharing the tricks of the trade that will help them reach their goal faster.

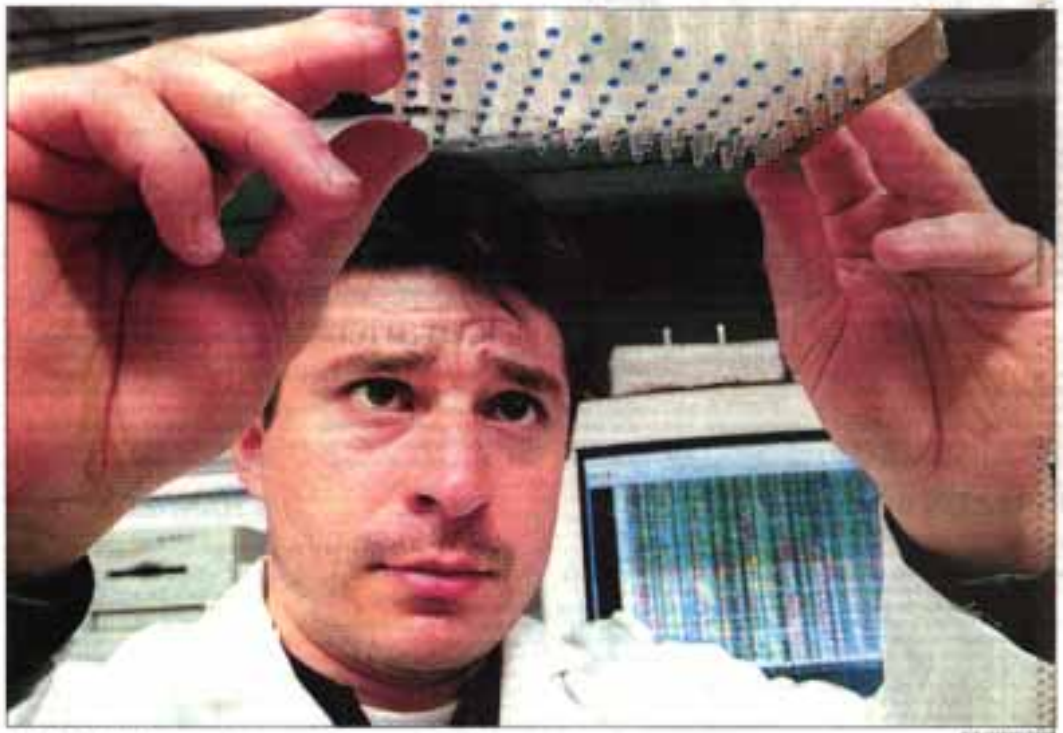
Right now, though, the researchers are still dealing with the details of relocating to a new office: getting to know their new neighbors across the hall, working out the quirks in the new computer lines, arranging poster-size "South Park" cutouts on the walls above their new machines and hiring a receptionist so visitors don't have to hang on the windows in hopes of finding someone to open the door.

By next year, they'll face some of these same problems again when the Department of Energy program expands into a second building, further consolidating operations from three national laboratories into one specially designed facility and nearly doubling its staff.

The department's collaboration, called the Joint Genome Institute, is its venture into the Human Genome Project, a worldwide effort to determine the order of more than 3 billion miniature parts of a person's DNA, known as bases or base pairs. Together these bases serve as the blueprint for our genes.

Specifically, the Joint Genome Institute is examining three of the 23 chromosomes that make up DNA.

See GENES, Page A24



LOLO CARDENAS holds a module containing 96 samples of DNA materials that will be analyzed by a computer.

The Joint Genome Institute's Production Sequencing Facility Walnut Creek, CA

- LLNL people
  - 8 supervisors
  - 45 staff

Genes associated with some human diseases are also found in other species.

Human Disease	Mouse	Fruit Fly	Worm	Yeast	Bacteria
Cystic Fibrosis	X	X	X	X	X
Myotonic Dystrophy	X	X	X	X	
Achondroplasia	X	X	X	X	
Amyotrophic Lateral Sclerosis		X	X	X	X
Bloom Syndrome			X	X	X
Huntington Disease	X				
Colon Cancer (Non-polyposis)	X	X		X	X
Pancreatic carcinoma		X	X		

These species become useful models to study the genetics of human disease.

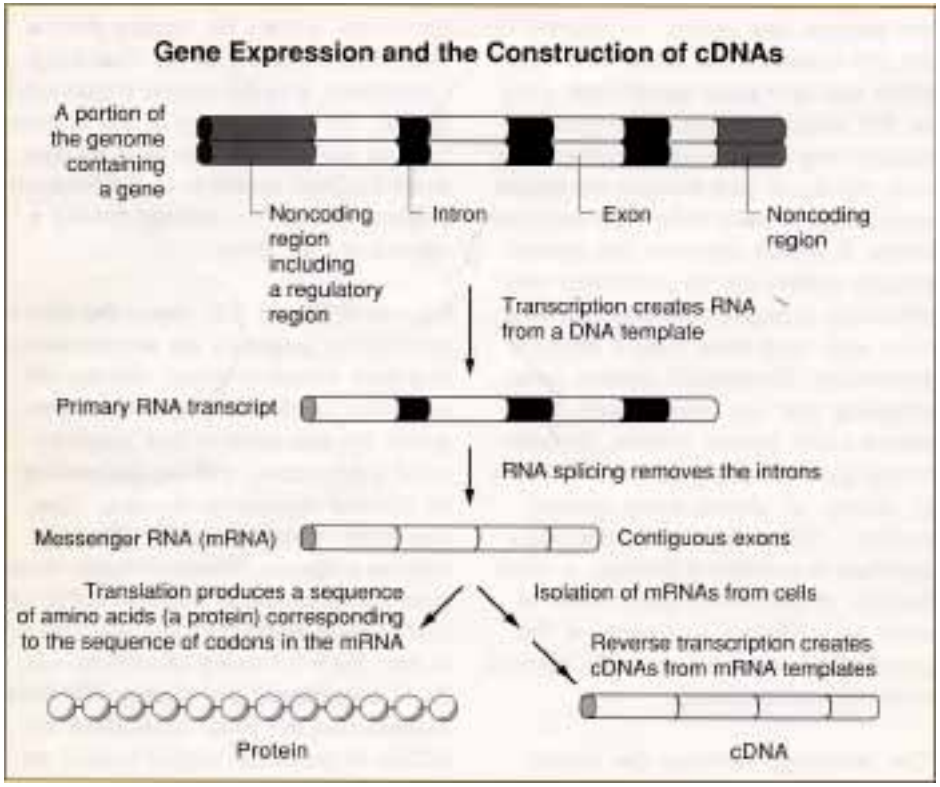
The I.M.A.G.E. Consortium: An Integrated Molecular Analysis of Genes and their Expression

Multiple groups working collaboratively to produce a publicly-accessible cDNA resource (libraries, clones, sequence)

The largest public collection of cDNAs in the world - 3.7 million clones from 5 species

All clones and sequence are publicly available!

What is a cDNA?



Overview of the IMAGE project

cDNA libraries

↓

Array 100 384-well plates/week

Make three copies of each plate

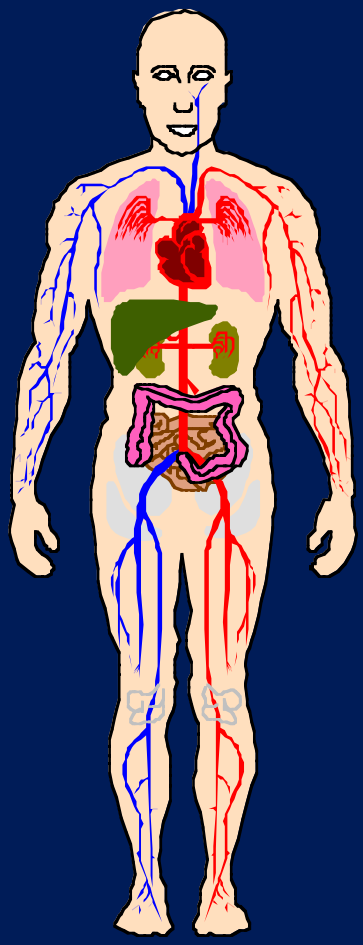
↙ ↓ ↘

sequencers, LLNL, distributors

The IMAGE Consortium has arrayed over 3.7 million clones from 340 human (43 tissues) and 97mouse (24 tissues) libraries.

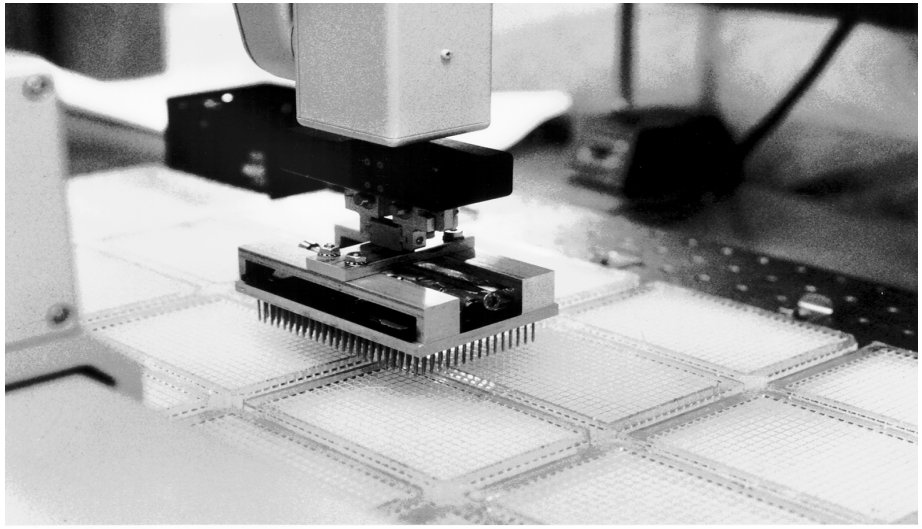
http://image.llnl.gov

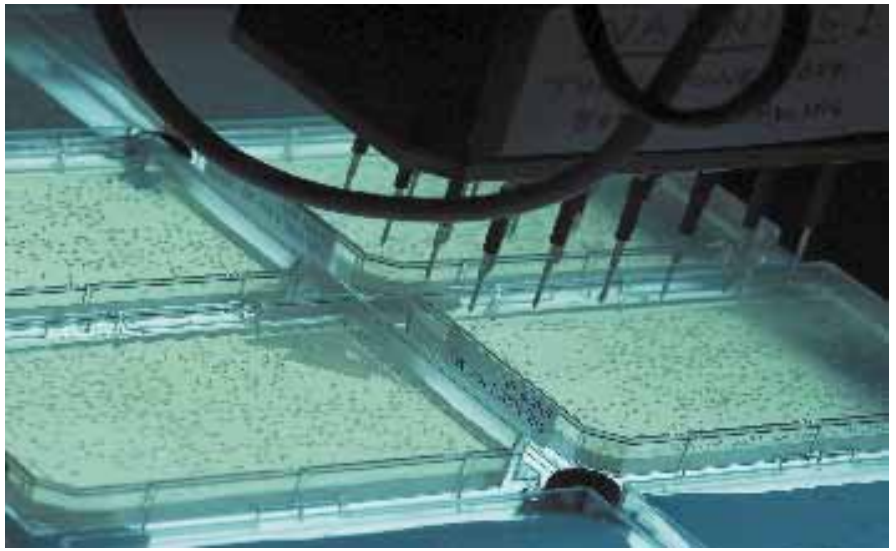
- Adipose
- Adrenal
- Alveolus
- B Cell
- Bone
- Bone Marrow
- Brain
- Breast
- Cervix
- Cochlea
- Colon
- Endothelial Cell
- Eye
- Fetus (total)
- Fibroblast
- Germ Cell
- Heart
- Kidney
- Larynx
- Liver & Spleen
- Leukocyte
- Lung



- Lymph Node
- Muscle
- Olfactory Epithelium
- Ovary
- Pancreas
- Parathyroid
- Peripheral Nervous System
- Pheochromocytoma
- Pineal Gland
- Placenta
- Prostate
- Uterus
- Pooled Organs
- Schwanomma Cell
- Skin
- Soft Tissue
- Spleen
- Stomach
- Thymus
- Thyroid
- Wilm's Tumor

Robots do the work!





Why is this resource important?

1. Gene discovery
   - Where and when are genes expressed?
   - How do genes relate to disease?

2. Functional analysis
   - What proteins are encoded?
   - What do they do?
   - How do they interact with other proteins?

Proteins are the workhorses of our body!

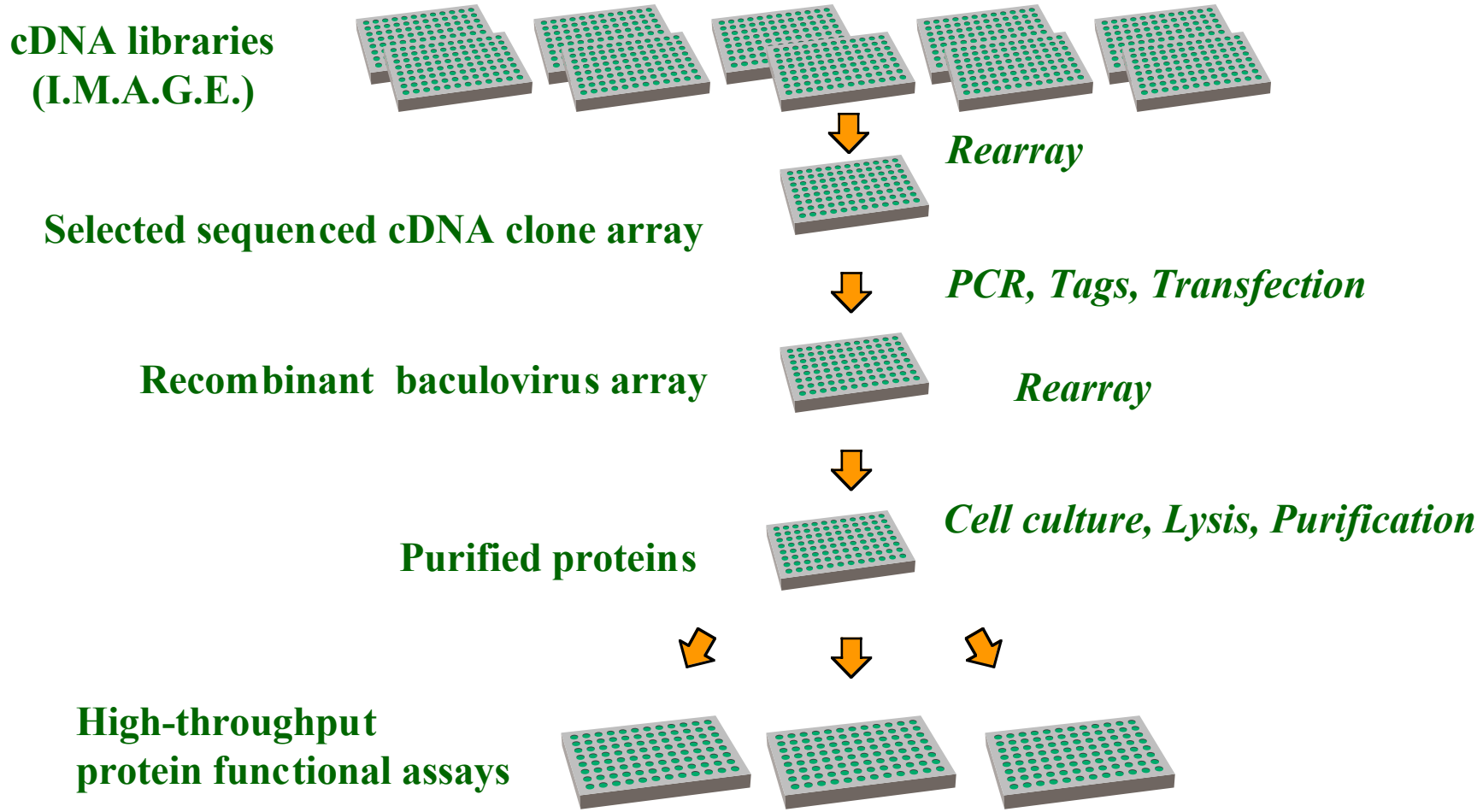
Genes → Proteins → Function

An individual's genes/proteins play a major role in:

- **response to exposure; and**
- **susceptibility/resistance to disease.**

Biosciences in the 21st Century will see a much greater emphasis on the study of protein structure and function.

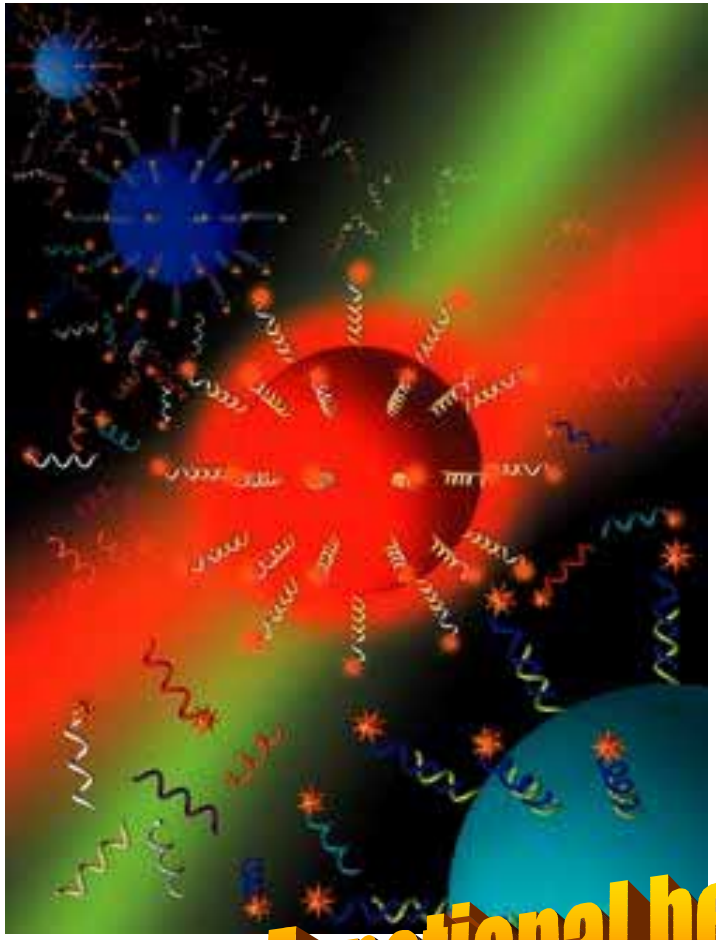
High-throughput Protein Production

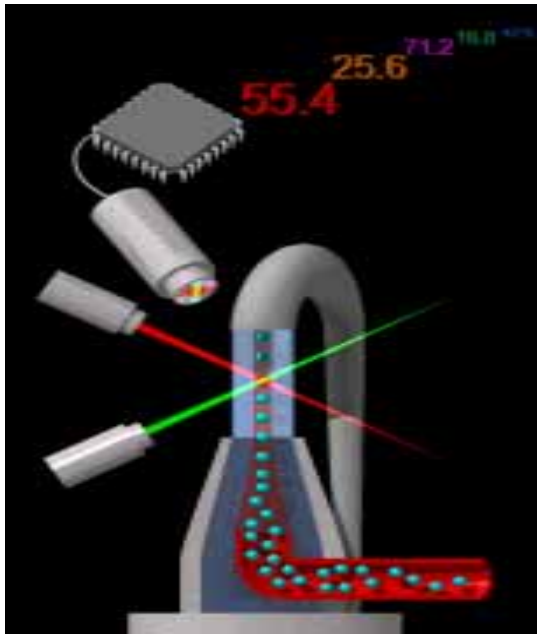


A genomics approach: high-density, array-based assays

DNA-DNA	genetic mapping physical mapping gene discovery
DNA-RNA	gene expression gene discovery gene regulation
DNA-Protein	sites of regulation
Protein-Protein	epitope mapping interactions
Protein/DNA vs chemicals	inhibitors enhancers

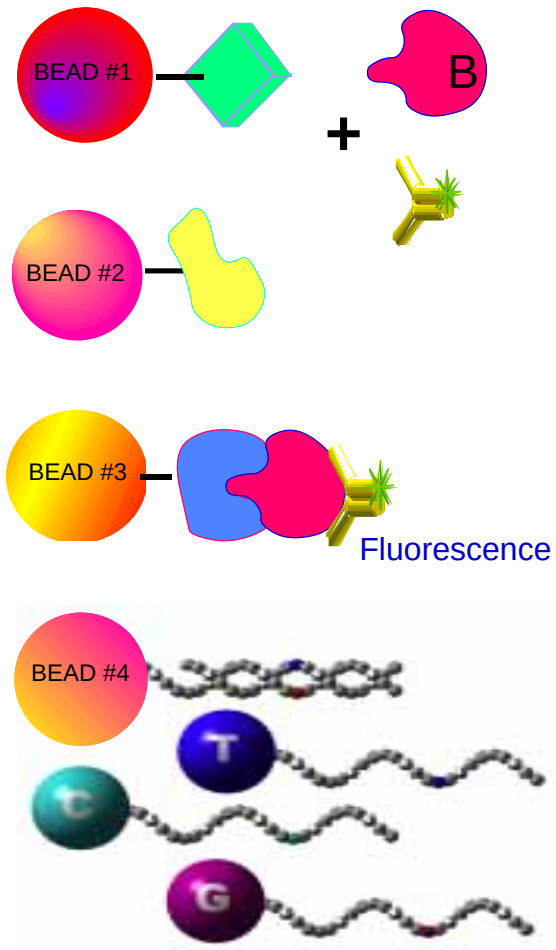
Dynamic liquid array identifies Protein Interactions





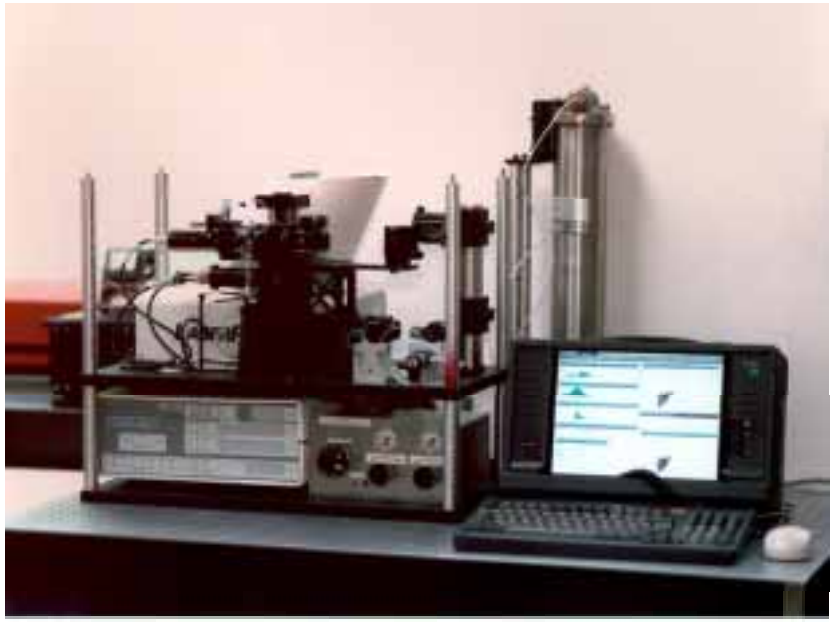
Functional bead assay

High-throughput Protein Functional Assays



We have designed and built several instruments for diagnostics and research

Portable “real-time” PCR



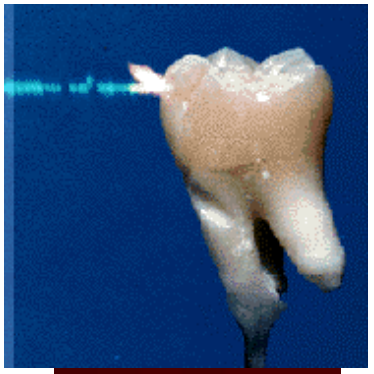
Healthcare Technologies

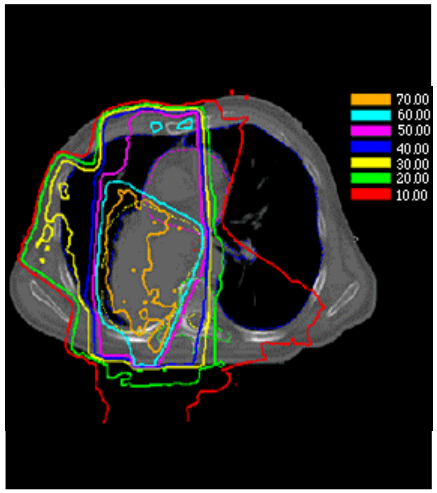
- *develop novel cost-effective healthcare technologies*
- *coordinate research and marketing LLNL-wide*
- *to some extent market-driven*

Micro-grippers

Stroke treatment

Lasers in medicine





Radiation therapy

Ergonomics laboratory

Mammography

Ethical, Legal, and Social Issues (ELSI)

Genetic Testing

- Should we offer tests to people if there is no treatment?
- Should we offer tests to people if the results cannot be certain?

Insurability

- Should people be denied heath coverage because of their genes?
- Should the person or society be asked to pay a higher rate?

Employment

- Should employers deny a job because of a genetic predisposition?

Criminal Justice

- Should a person be held criminally liable if his/her behavior has a genetic basis?

Education

- Do we ignore these issues or become proactive?